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Outcome of relapse in lupus nephritis: Roles of reversal of renal fibrosis and response of inflammation to therapy

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Outcome of relapse in lupus nephritis: Roles of reversal of renal fibrosis and response of inflammation to therapy.

Background. Renal relapse in lupus nephritis has been shown to have ominous prognostic significance with the majority of patients progressing to doubling of serum creatinine (CRX2). However, not all patients do so. This report explores the roles of response of inflammation to therapy and of glomerular scarring and interstitial fibrosis and their potential reversal to outcome of renal relapse.

Methods. Renal biopsies from 71 patients with lupus nephritis with an initial biopsy (Bx1) and systematic control biopsy (Bx2) after six months of therapy, as well as subsequent biopsies for clinical indications, were studied. The relationships of morphologic factors to renal relapse and its outcome as well as to CRX2 and end-stage renal disease (ESRD) were analyzed. Cox proportional hazards modeling was used to assess association of morphologic variables with outcomes.

Results. Renal interstitial fibrosis and glomerular segmental scarring were partially reversible in 17 and 11 patients, respectively. This decline was associated with an excellent prognosis, with only one patient in each group (5.9% and 9.1% respectively) progressing to CRX2. All 18 patients who progressed to CRX2 either failed to respond to therapy (7 patients) as defined by normalization of serum creatinine (S_{Cr}) and reduction of proteinuria to ≤1 g/day, or relapsed after initial response (11 patients), as defined by recent rise of S_{Cr} >50% and/or proteinuria >3.5 g/day. However, relapse also occurred in 11 of 47 other patients without progression to CRX2. These patients showed a greater initial response of inflammation and deposits to therapy and fibrous lesions partially reversed in the period prior to relapse, so that active lesions were superimposed on a lower level of chronic lesions. By contrast, chronic lesions mounted steadily in those who progressed to CRX2. Cox proportional hazards modeling indicated a strong association of inflammatory variables with renal relapse, CRX2 and ESRD. However, the extent of immunoglobulin deposits was not significantly associated with any outcome. Finally, we found that failure of disease to remit also is associated with a high rate of CRX2 (64.8% vs. 13.0%, $P = 0.00034$).

Conclusions. Interstitial fibrosis and glomerular scarring in systemic lupus erythematosus are partially reversible, and this reversal is attended by an excellent outcome. The outcome of renal relapse is determined by the initial response of inflammatory and chronicity elements to therapy, those with prior partial reversal of interstitial and glomerular scarring having a good outcome, and those in whom fibrotic lesions have continued to increase and have a poor outcome. Inflammatory variables appear to be more important in determining outcome than immunoglobulin deposits.

In studies reporting on 71 patients with initial and systematic six-month biopsies after induction treatment, we found that the initial biopsy had very little predictive ability [1, 2]. However, at the six-month biopsy a number of morphologic variables were predictive of progression to doubling of the serum creatinine (CRX2) and end-stage renal disease (ESRD). In ascending order of predictive strength, these included persistent subendothelial and mesangial deposits (as reported by others as well [3]), overall immune deposits (particularly C3) by immunofluorescence (IF), and most importantly, the ongoing presence of inflammatory elements, such as cellular crescents and macrophages in the tubular lumens. However, a bothersome question is why the results of a biopsy at six months can be predictive of events that might occur as much as five to ten years in the future, with numerous clinical events intervening in the meantime, particularly renal relapse [4, 5] or the failure to go into remission [6], both of which have been shown to be major risk factors for progression. This study investigates the factors that determine whether or not a patient with a renal relapse will progress to CRX2.

An allied issue was the role of fibrotic lesions in progression. Intuitively, one would anticipate that the level of chronic lesions would be predictive of outcome, and a number of groups indeed have found this to be the case

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[7–16]. In our studies, though, they were not predictive at either Bx1 or Bx2. Further study reveals they do play a role, but not in the manner anticipated.

METHODS

Patient population

Renal biopsies and clinical data from 71 patients from four Paris hospitals (Bichat, St. Louis, Broussais, and Henri Mondor) from the period 1986 to 1994 were evaluated. The patients were involved in a protocol for treatment of lupus nephritis, the majority (55 patients) with WHO Class IV lesions on initial biopsy, but also nine patients with relatively extensive Class III lesions and seven patients with mixed membranous and proliferative (Class Vc and Vd) lesions according to the 1982 WHO criteria [17]. Cases were accepted as diffuse proliferative lupus nephritis with as few as five glomeruli provided all five showed proliferative lesions. No case of focal proliferative GN or of mixed membranous and focal proliferative GN was diagnosed with fewer than ten glomeruli. The mean number of glomeruli/biopsy did not differ significantly between the three biopsies, ranging between 16.5 ± 9.9 to 20.4 ± 12.0. On Bx2 and Bx3, the minimum number of glomeruli for each biopsy was four, with 164 of 174 (94.3%) biopsies in the study having seven or more glomeruli. Criteria for acceptance of cases into the study and demographic distribution are given in a prior communication [1].

All patients had an initial renal biopsy (Bx1), followed by six-month induction treatment consisting of monthly intravenous cyclophosphamide [0.7 g/m^2 body surface area (BSA)] combined with prednisone (0.9 ± 0.4 mg/kg body weight/day for one month tapered to 0.4 ± 0.1 mg/kg body weight/day at 6 months) in 58 patients, and corticosteroids alone in 13 patients (1.4 ± 0.3 mg/kg body weight/day tapered to 0.5 ± 0.16 mg/kg body weight/day at 6 months). Initial treatment was followed at six months by control renal biopsy (Bx2) to evaluate the effects of therapy. Subsequent biopsies were performed primarily for clinical indications, with some patients having as many as five biopsies total. Follow-up varied from 4.5 years to 12.5 years, with an average of 7.0 years.

Technical methods and record review

Specifics of the technical methods are given in a prior communication [1]. Briefly, light microscopic slides were prepared and stained according to standard methods for light and IF microscopy. All IF material reported in this study was processed at the Hôpital Broussais, all positive antisera were reviewed with systematic photography, and the data reported by the same personnel. All biopsies were evaluated in random order by a pathologist (GSH) who was blind to the clinical data. Similarly, the IF photos were reviewed separately in random order by the same pathologist.

Standard clinical parameters were evaluated at the time of each biopsy as previously reported [1, 2]. Clinical data were available for all patients for the initial two biopsies; however, the follow-up data as to outcome were incomplete for six patients (2 focal, 3 diffuse, and 1 mixed membranous and proliferative).

The following definitions were used regarding treatment and response.

Therapeutic response. Defined as reduction of proteinuria to ≤1 g/day and normalization of serum creatinine (S_{Cr}). Hematuria, not included in the definition, also was reduced to ≤10,000 red blood cells (rbc)/mL in all but two patients, one who went on to CRX2 and one who did not, although this reduction in hematuria frequently took more time than the reduction in proteinuria.

Renal relapse. Relapse was defined as recrudescence of renal disease after an initial therapeutic response shown by a recent increase of S_{Cr} by >50% with active urinary sediment (nephritic relapse) or increase in proteinuria to 3.5 g/day or greater (nephrotic relapse). Cases with nephritic relapse frequently had elevations, sometimes marked, in proteinuria as well [4].

Renal remission. A reduction of proteinuria to ≤0.33 g/day and S_{Cr} to ≤123 μmol/L at any point in the course defined remission.

Three outcome parameters were evaluated in this study: (*1*) Doubling of the initial serum creatinine (CRX2) for three months or more, the outcome measure used in a number of recent studies in lupus nephritis [4, 5, 7–9, 18–20]; (*2*) ESRD requiring dialysis and/or transplant; (*3*) final renal function (RF_{last}), with the last S_{Cr} measurement having an arbitrary value of 500 μmol/L assigned to all patients with ESRD, whether they were on dialysis or transplanted.

Morphologic variables

The schema for evaluation of morphologic variables has been reported in detail in our earlier studies [1, 2]. Briefly, the method of grading morphologic lesions parallels that used by Austin et al, using the same grading system of 0 to 3+, but adding consideration of tubular lesions and IF data [7]. The definitions of Austin et al were strictly applied for the standard variables [7] with the exception of glomerulosclerosis, which was divided into totally sclerotic glomeruli and glomeruli with segmental scars, with each being recorded separately. In the Biopsy Index, glomerular and tubular macrophages were estimated semiquantitatively from routine stains, and subsequent studies have shown these semiquantitative estimates to have an excellent correlation with macrophages stained for CD68 (PGM1) and counted morphometrically [2].

An Immunofluorescence Index (IFI) was devised in

the following manner. Antisera to the following were employed in all cases: IgG, IgA, IgM, C3, C1q, and fibrinogen. Four separate morphologic IF components were evaluated: glomerular capillary, glomerular mesangial, vascular, and tubulointerstitial. Staining for each antiserum was graded on a scale of 0 to 4+ for each component, relying primarily on extent rather than brightness. The totals for all the antisera were then added for a maximum of 24 for each component. In addition to the IFI, total staining for each antiserum was calculated, for a maximum of 16/antiserum. In addition, glomerular capillary deposits were divided by location, subendothelial versus subepithelial, on photographs of the IF, as described previously [2].

Arterial and arteriolar light microscopic lesions are not included in this study because their correlations with clinical and outcome variables are relatively weak [1]. In this study only vascular IF was included. The Biopsy Index and its abbreviations are delineated in Table 1. In addition, the composite variables of total immunoglobulin deposits (Total Ig = IgG + IgA + IgM) and biopsy inflammation (BxInfl = kary/fib + cresc + glmonos + tubmacr + intinfl) are used extensively throughout this article.

Statistical analyses

For correlations between variables, Pearson product-moment correlation coefficients or Spearman rank order correlations were used as appropriate, as previously described [1, 2]. The influence of multiple morphologic variables on the risk of renal relapse, CRX2 and ESRD was assessed using the Cox proportional hazards regression model, using only cases with complete light microscopic, IF, and follow-up data. Comparisons of survival were done by the Kaplan-Meier method, with differences in survival curves evaluated by log rank sum testing.

Table 1. Components of the Biopsy Index

	Abbreviation	Scale
Glomerular Activity Index (GAI)		
Glomerular proliferation	glprolif	0–3+
Polymorphonuclear leukocytes	glpmn	0–3+
Karyorrhexis/Fibrinoid necrosis	karyfib	(0–3+) X2
Cellular crescents	cresc	(0–3+) X2
Hyaline deposits	hyaldep	0–3+
Glomerular monocytes	glmono	0–3+
		Maximum: 24
Tubulointerstitial Activity Index (TIAI)		
Tubular cell pyknosis	tubpyk	0–3+
Tubular nuclear 'activation'	tubact	0–3+
Tubular cell necrosis	tubnec	0–3+
Tubular cell flattening	tubflat	0–3+
Macrophages in tubular lumens	macrlum	0–3+
Epithelial cells in tubular lumens	eplum	0–3+
Interstitial inflammation	intinfl	0–3+
		Maximum: 2
Chronicity Lesions Index (CI)		
Glomerulosclerosis	glscl	0–3+
Glomerular scars	gloscar	0–3+
Fibrous crescents	fibcres	0–3+
Tubular atrophy	tubatro	0–3+
Interstitial fibrosis	intfib	0–3+
		Maximum: 15
Immunofluorescence Index (IFI)		
Glomerular capillary IF	glcapif	(0–4+) X6 antisera
Glomerular mesangial IF	glmesif	(0–4+) X6 antisera
Tubulointerstitial IF	tubulif	(0–4+) X6 antisera
Vascular IF	vascif	(0–4+) X6 antisera
		Maximum: 96

$$\text{Biopsy Index} = \frac{\text{GAI}}{8} + \frac{\text{TIAI}}{7} + \frac{\text{CLI}}{5} + \frac{\text{IF Index}}{32} = \text{Maximum } 12$$

The Biopsy Index is comprised of each of the individual indices, normalized to 3 maximum by division by appropriate number of components.

Biopsy Inflammation (BxInfl) = glpmn + karyfib + cresc + glmono + tubmacr + intinfl

Total Immunoglobulin (Total Ig) = IgG + IgA +IgM

RESULTS

Changes in the Chronic Lesions Index (CLI) and its variables during therapy

Cases were divided into those who doubled their S_{Cr} (CRX2) levels and those who did not (No CRX2). As anticipated, overall the CLI and its component variables progressively increased in severity (Fig. 1). However, in a number of cases these variables decreased rather than increasing from one biopsy to the next. These cases were largely confined to the No CRX2 group, where in three instances there was a steady decrease over three successive biopsies (from Bx1 to Bx3 in 2 instances and from Bx2 to Bx4 in the third).

Interstitial fibrosis. Table 2 compares 17 patients in whom there was a decrease in interstitial fibrosis (Intfib↓) with 28 patients whose fibrosis increased (Intfib↑) from Bx1 to Bx3 (or Bx2 for cases with no third biopsy). Although proteinuria was roughly equal in the two groups at Bx1, at Bx2 those who progressed still had substantial proteinuria, whereas the Intfib↓ group had largely cleared their proteinuria. Importantly, tubular epithelial lesions decreased in the Intfib↓ patients, but remained high in the Intfib↑ group. Furthermore, other morphologic variables tended to move in parallel with interstitial fibrosis. The Intfib↓ group had an excellent outcome, with only one patient (5.0%) going on to CRX2. By contrast, the Intfib↑ group had a parallel increase in other parameters, and had a high rate of CRX2 and ESRD. Sampling error as an explanation for the overall differences was ruled out by χ^2 testing for distribution between groups of CRX2 ($P = 0.00002$) and ESRD ($P = 0.00001$).

Glomerular scars. Similarly, in 11 patients there was a reduction in segmental glomerular scarring (Gloscar↓)

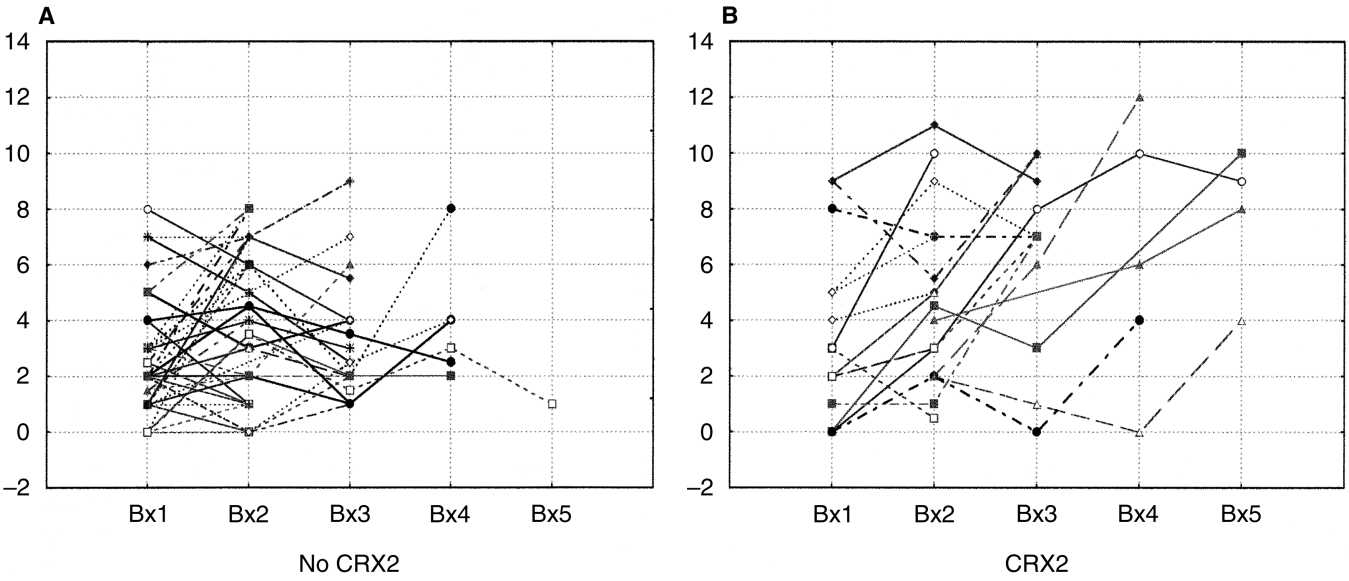

Fig. 1. Chronic Lesions Index in the (*A*) no serum creatinine doubling (No CRX2; *N* = 47 patients) and (*B*) serum creatinine doubling (CRX2; *N* = 18 patients) groups. Note that a number of cases diminish the severity of chronic lesions in the No CRX2 group, whereas they mount progressively in the CRX2 group.

Table 2. Comparison of cases with decrease versus increase of interstitial fibrosis

	Interstitial fibrosis		
	Decreases (17 patients)	Increases (28 patients)	*P*
Proteinuria–Bx1	4.3 ± 3.5	5.4 ± 3.4	NS
Proteinuria–Bx2	0.7 ± 0.8	2.0 ± 2.7	0.03
Proteinuria–Bx3	1.4 ± 2.2	3.4 ± 2.6	0.07
S_{Cr}–Bx1	95 ± 33	127 ± 43	0.01
S_{Cr}–Bx2	83 ± 14	112 ± 62	0.08
S_{Cr}–Bx3	86 ± 16	132 ± 64	0.08
ESRD	0.00%	28.6%	0.02
CRX2	5.9%	35.7%	0.03
RFlast	115 ± 89	231 ± 187	0.02
Interstitial fibrosis 1	0.97 ± 0.56	0.44 ± 0.54	0.004
Interstitial fibrosis 2	0.63 ± 0.54	1.26 ± 0.68	0.002
Interstitial fibrosis 3[a]	0.62 ± 0.44	1.68 ± 0.93[c]	0.007
Interstitial inflammation 1	1.31 ± 0.60	1.27 ± 1.03	NS
Interstitial inflammation 2	0.42 ± 0.55	0.80 ± 0.64	0.05
Interstitial inflammation 3[a]	0.31 ± 0.37[c]	1.46 ± 1.17	0.01
Tubular epithelial 1[b]	3.65 ± 1.89	4.57 ± 2.76	NS
Tubular epithelial 2	2.03 ± 1.70	4.74 ± 2.38	0.0002
Tubular epithelial 3[a]	1.75 ± 1.28[c]	4.71 ± 3.12	0.02
Chronic Lesions Index 1	2.72 ± 2.11	2.02 ± 1.99	NS
Chronic Lesions Index 2	2.35 ± 2.08	4.67 ± 2.56	0.003
Chronic Lesions Index 3[a]	2.37 ± 1.62	5.53 ± 2.95[c]	0.006
Biopsy inflammation 1	4.59 ± 2.17	6.59 ± 3.59	0.05
Biopsy inflammation 2	1.12 ± 1.49	2.22 ± 2.17	0.07
Biopsy inflammation 3[a]	0.56 ± 1.01[c]	3.25 ± 2.69[c]	0.01

The Table includes only patients with a complete follow-up. Decreases and increases are defined in terms of decrease/increase in interstitial fibrosis between Bx1 and Bx3, or between Bx1 and Bx2 if there is no third biopsy. Twenty patients had no net change in interstitial fibrosis between biopsies.

[a] At Bx3 there were only 8 biopsies in the decrease group and 14 biopsies in the increase group

[b] Tubular epithelial = tubpyk + tubact + tubnec + tubflat + eplum

[c] Differences between Bx1 and Bx3 significantly different ($P < 0.05$) for that group

between Bx1 and Bx3 (or Bx2 for cases with no Bx3). Comparison with 30 patients in whom glomerular scars increased (Gloscar↑) revealed that although there were no significant differences in either proteinuria or S_{Cr} at any of the three biopsies, the outcome was much more favorable in the Gloscar↓ group, with a lower rate of CRX2 (9.1 vs. 40.0%, $P = 0.06$) and lower final S_{Cr} value (119 ± 134 vs. 248 ± 190, $P = 0.04$).

This diminution of glomerular scarring appears to be real. First, sampling error was once again ruled out by χ^2 testing for CRX2 ($P = 0.000000$). Secondly, interstitial fibrosis was significantly lower at Bx3 in the Gloscar↓ group (0.87 ± 0.69 vs. 1.69 ± 0.90, $P = 0.0415$). Finally, global glomerulosclerosis also was lower in the Gloscar↓ group (0.75 ± 1.16 vs. 1.08 ± 0.86, NS), arguing against progression of scars to global glomerulosclerosis as the explanation for the decline. As with Intfib↓ patients, tubular epithelial lesions and biopsy inflammation are significantly lower in the Gloscar↓ group.

Role of response to therapy and renal relapse in progression

Not surprisingly, failure to respond to therapy (defined as proteinuria ≤1 g/day and normalization of S_{Cr}) was attended with a disastrous outcome. Seven of nine patients who failed to respond went on to CRX2. The remaining two patients died in renal insufficiency (S_{Cr} = 325 and 360 μmol/L, respectively) but did not technically double their S_{Cr} value for the requisite three months.

For those who responded initially, renal relapse was a major risk factor for progression to CRX2 (Fig. 2). Of the 56 patients who responded to therapy, all of those who progressed to CRX2 (11 patients) had subsequent

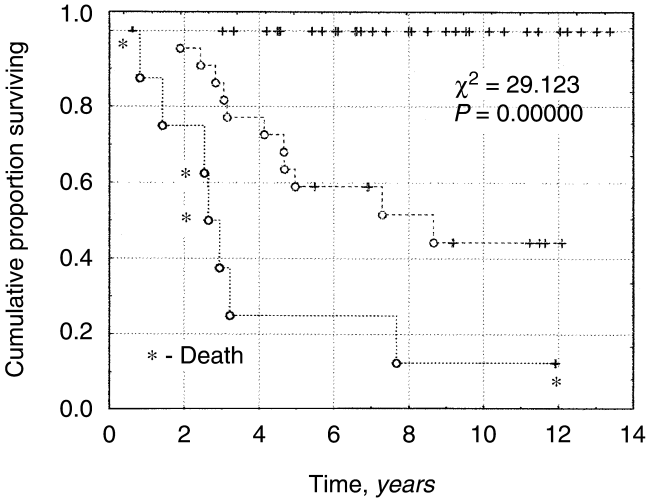

Fig. 2. Ten-year survival rate from CRX2 showing therapeutic response and renal relapse. Symbols are: (solid line) Response-No Relapse; (dotted line) Response-Relapse; (dashed line) No Response; (○) complete; (+) censored. The percentages are: Response-No Relapse, 100%; Response-Relapse, 42.7%; No Response, 12.7%. Survivals are calculated from time 0, but curves begin at first event, completion or censoring. Asterisks indicate patient deaths and are confined to the No Response group. Both patients in this group who did not technically qualify as doubling their S_{Cr} for 3 months or more, nonetheless died in marked renal insufficiency (S_{Cr} = 325 and 360 μmol/L, respectively).

renal relapses versus 11 relapsing patients among the 45 patients who did not progress to CRX2 (P = 0.0058). Nephritic relapses were more frequent and had a worse prognosis than those with proteinuric relapses: 10 of 16 nephritic relapses versus 1 of 8 patients with proteinuric relapses went on to CRX2 (P = 0.02).

We compared the CRX2 group with the No CRX2 group, which was subdivided into those who did relapse (Relapse-No CRX2) and those who did not (No Relapse-No CRX2). We compared data at the first, second and third biopsies (excluding 2 patients whose 3rd biopsies were not contemporaneous with their relapse). Differences in clinical values among the groups were modest. The Relapse-No CRX2 group showed lower CH_{50}, and greater hematuria and proteinuria at Bx1 and greater hematuria at Bx2 than the No Relapse-No CRX2 group. At Bx3, the No Relapse-No CRX2 group had less proteinuria than the two groups with relapse.

The morphologic differences are easiest appreciated graphically. Figure 3A shows the relative values for Total Ig and C3 deposits, and Figure 3B those for BxInfl. For easier comparison, values are indexed such that the values at Bx1 for the No Relapse-No CRX2 group = 1. Several points should be made: (*1*) Values for patients destined to CRX2 started at slightly higher means at Bx1, but only the differences in C3 were statistically significant. (*2*) At Bx2, the values for both sets of parameters declined, but those for the No CRX2 groups declined much more dramatically than those for CRX2. (*3*) In all instances the declines were much greater for BxInfl than for IF variables at BX2. (*4*) At the time of renal relapse at Bx3 there was a recrudescence of IF variables and BxInfl in both the CRX2 and Relapse-No CRX2 groups. In contrast, these parameters continued to decline in the No Relapse-No CRX2 group. (*5*) Data at Bx4 were limited, and there were only five biopsies in the CRX2 group and three in the No Relapse-No CRX2 group, but they suggest that once again deposits and inflammation were reduced more in the No Relapse-No CRX2 group than in the CRX2 group (Fig. 4).

Some specific comments should be added regarding the contrasting behaviors of Total Ig and C3 (Fig. 3A). Behavior of Ig deposits did not differ greatly between the three groups. However, C3 in the CRX2 group differed substantially; it started at Bx1 at significantly higher levels and declined by much less at Bx2. Finally, relapse was marked in both groups by much greater relative changes in C3 than Ig deposits.

Examination of the Chronic Lesions Index (CLI; Fig. 3C) at the three biopsies gives some insight into why—despite similar levels of active lesions at Bx3—the *CRX2* group progressed to renal insufficiency whereas the Relapse-No CRX2 group did not. In the CRX2 group the CLI continued to mount between Bx2 and Bx3, whereas in both of the No CRX2 groups it actually declined.

Role of remission in progression

The influence of remission, defined by Korbet et al as $S_{Cr} \leq 123$ μmol/L and proteinuria less than 0.33 g/24 h [6], was examined on outcome. We found that remission was associated with an 87.0% 10 year survival from CRX2 versus 35.1% for those who did not remit (P = 0.00034).

Morphologic factors associated with renal relapse and progression to CRX2 and ESRD

At the time of the initial biopsy, the sole morphologic variables predictive of future behavior were vascif and C3 [1, 2]. Univariate analysis at Bx2 revealed a number of variables associated with subsequent relapse and progression (Table 3). Cox proportional hazards modeling was performed to ascertain the association of these variables with renal relapse, CRX2 and ESRD (Table 4). To have a global impression for the relative significance of immunoglobulin deposits, inflammatory lesions, and chronic lesions, the composite variables of Total Ig, BxInfl, and CLI were used. Prior survival analyses had revealed that each of the composite variables was a stronger predictor than any of its individual components or any lesser combination of them [2].

BxInfl was highly associated with all three outcomes with very respectable βs, but Total Ig had weak βs, none of which was significant. Chronic lesions were not significantly associated with any outcome and only at Bx3 were they finally significantly associated with CRX2 (β =

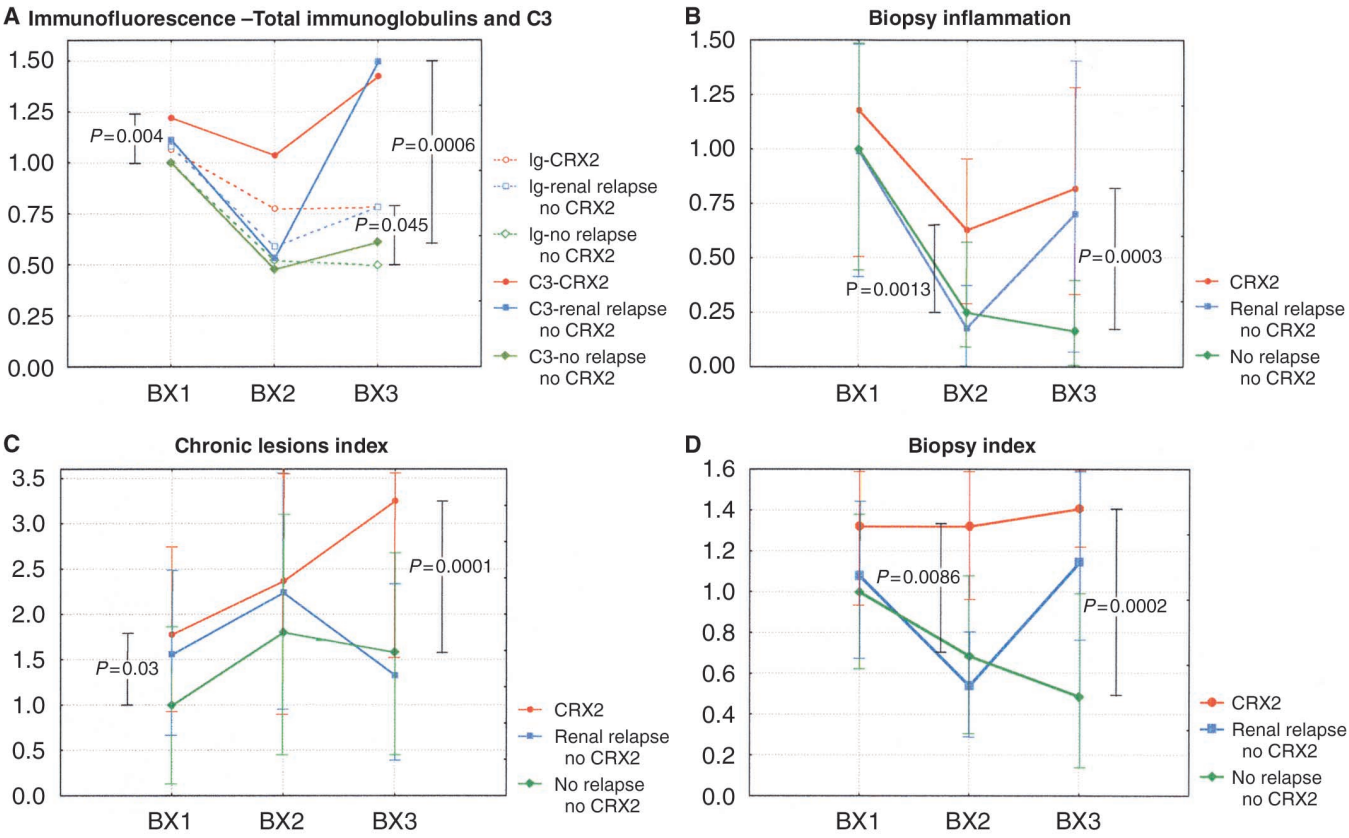

Fig. 3. Comparisons of CRX2, Renal Relapse–No CRX2, and No Relapse-No CRX2 groups. (*A*) Total immunoglobulins and C3. (*B*) Biopsy inflammation. (*C*) Chronic Lesions Index. (*D*) Biopsy Index. Note that response to treatment at Bx2 is much greater for both Total Ig and C3 and BxInfl in the Relapse-No CRX2 and No Relapse-No CRX2 groups. Relapse at Bx3 shows increase of both C3 and BxInfl. In panel C, the chronicity elements decline in the two No-CRX2 groups but continue to mount in the CRX2 group. The Biopsy Index, in effect a summation of the active and chronic components, remains high throughout in the CRX2 group, but descends in the No CRX2 groups.

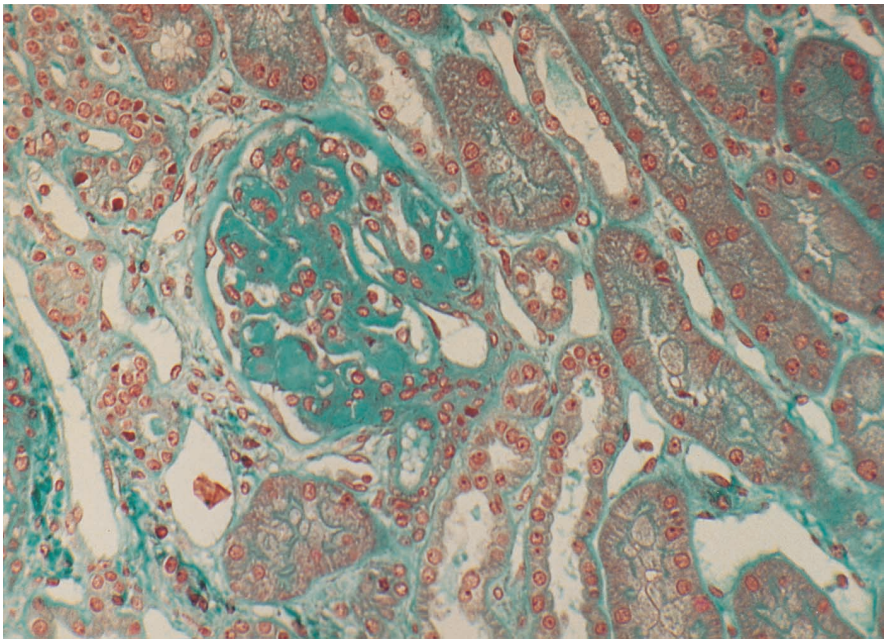

Fig. 5. Glomerulus with massive hyaline deposits and intracapillary coagula but minimal inflammation. Intraglomerular proliferation and inflammation are nearly absent, and there is almost no surrounding interstitial inflammation. Periodic acid-Schiff (PAS) stain; ×350.

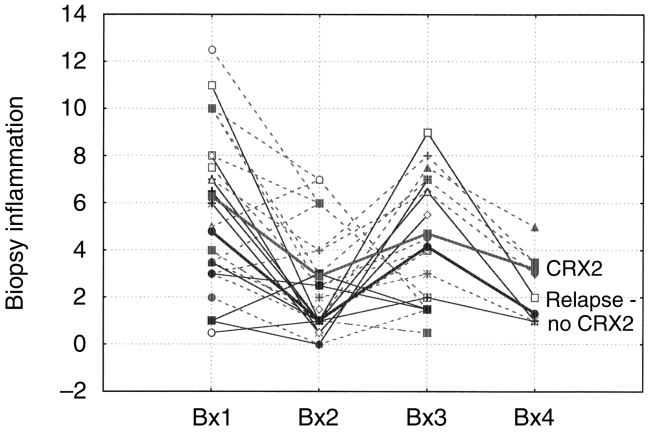

Fig. 4. Biopsy inflammation in the CRX2 and Renal Relapse-No CRX2 Groups. Symbols are: (dotted lines) CRX2; (solid lines) Renal Relapse-No CRX2; (thick solid lines) group means. BxInfl responds to therapy significantly better in the Renal Relapse-No CRX2 group at Bx2 and likely does so again at Bx 4, but data are too limited to be significant. (The No Relapse-No CRX2 group is excluded from consideration).

0.3363, $P = 0.01$). In contrast with Total Ig, the βs of C3 deposits were significantly associated with all three outcomes, increasing with worsening outcomes. Other individual associated variables were either inflammatory in nature, or in the instance of epithelial cells in tubular lumens, reflected ongoing tubular damage.

Relative dissociation of glomerular hyaline deposits and inflammation

As has been described by others [17] and noted by virtually everyone, we observed that there were a number of cases at Bx1 of diffuse proliferative disease with massive hyaline subendothelial and intracapillary deposits but with limited proliferative and inflammatory lesions (Fig. 5). These cases, defined as those with 3+ hyaline deposits and BxInfl <7.0 (mean value for cases with diffuse proliferative lesions) were compared with the remaining cases of diffuse proliferative lupus (Table 5). Clinically, they differed significantly only at the last biopsy, Bx3. However, the outcome in the group with massive deposits but little inflammation was much better, with no ESRD (vs. 35.2% for the remaining cases, $P = 0.013$) and better final renal function ($S_{Cr} = 100 \pm 62$ vs. 261 ± 199 μmol/L, $P = 0.0044$). Morphologically, the most striking difference was the milder tubular epithelial lesions in the massive deposits group, both at Bx1 and Bx2. The inflammation also tended to respond better to therapy at Bx2 and Bx3.

Relative lack of overlap between groups with good prognostic features

Four groups were found to have a good prognosis in this study: the Intfib↓ patients, the Gloscar↓ group, those with initial marked hyaline deposits but little inflammation, and those with no history of renal relapse. A legitimate concern is that these might be overlapping variables, all describing basically the same group of patients with good prognosis. Morphologically this is not the case. As might be expected, there was overlap between the Intfib↓ and Gloscar↓ groups; four patients fell into both groups out of 11 and 17 patients, respectively. However, only three patients (5.6%) had both initial marked deposits and a decrease in interstitial fibrosis, compared to 4.6% who would be predicted statistically if these were independent variables. Nor is this the case for the clinical variable, lack of renal relapse. Compared to the overall incidence of renal relapse (33.8%), the marked hyaline deposits group had 35.7% relapses (NS), the Gloscar↓ group 37.3% (NS), and the Intfib↓ group 29.7% (NS).

DISCUSSION

Diminution of interstitial fibrosis and glomerular sclerosis

There is a tendency to think of glomerular and interstitial fibrosis as cumulative and immutable, despite the fact that it is known that the amount of extracellular matrix (ECM) depends on the balance between its accumulation and its degradation. Degradation of ECM depends on metalloproteinases (MMPs) and plasmin that degrade collagen and other matrix components, and is countered by tissue inhibitor of metalloproteineases-1 (TIMP-1) and plasminogen activator inhibitor-1 (PAI-1), which block degradation as these inhibitors are associated with an influx of macrophages [21–23]. In most instances the balance between accumulation and degradation is altered in favor of progressive fibrosis. However, clear cut reversal of glomerular sclerosis and interstitial fibrosis has been demonstrated in several animal models [24–28]. Specifically, as regards MMPs and their inhibitors, in one study of puromycin aminonucleoside (PAN) nephrosis [24], a single injection of PAN led to fibrosis early on that was accompanied by up-regulation of TIMP-1, although MMPs remained relatively constant, followed by resolution of the fibrosis over several weeks with diminution in TIMP-1 as fibrosis resolved.

In our study a number of cases showed diminution of the extent of interstitial fibrosis and glomerular sclerosis over successive biopsies (Fig. 1 and Table 2). The cases with diminution in fibrosis also showed substantially less glomerular sclerosis, less interstitial inflammation, and better outcomes and final renal function than those whose interstitial fibrosis progressed (Table 2). It is reasonable to conclude that in these patients the balance between synthesis and degradation of ECM now favored degradation, and to speculate that this shifted balance represents primarily quiescence of TIMP-1 and PAI-1. The substantially lesser degree of interstitial inflammation in these patients supports this suggestion. (Obviously, in any given case, sampling error is a major consid-

Table 3. Variables significantly associated with renal relapse, CRX2, and ESRD at biopsy 2 univariate analysis

	Renal relapse		CRX2		ESRD	
	Beta	*P*	Beta	*P*	Beta	*P*
Composite variables						
Biopsy inflammation	0.27	0.003	0.59	0.0000	0.46	0.0003
Total Ig–IF	0.10	0.06	0.09	0.14	0.04	0.47
Individual variables						
Glomerular proliferation			0.56	0.03		
Glomerular PMNs	1.35	0.007	1.03	0.01		
Karyorrhexis/fibrinoid necrosis	1.03	0.003	0.94	0.0007		
Cellular crescents			1.77	0.001	2.00	0.00006
Glomerular monocytes	0.66	0.05	0.83	0.009		
Fibrous crescents			1.00	0.05	1.28	0.02
Glomerular scars			0.58	0.05	0.58	0.06
Tubular nuclear activation			0.81	0.02		
Macrophages–tubular lumens			2.72	0.0003	2.23	0.003
Epithelial cells–tubular lumens			0.96	0.01	0.76	0.06
Interstitial inflammation	0.51	0.006				
Glomerular capillary IF	0.20	0.002	0.14	0.02		
Vascular IF	0.20	0.03	0.24	0.02		
Tubular IF	0.19	0.003	0.16	0.02		
IgG–IF	0.18	0.07	0.13	0.07		
C3–IF	0.31	0.006	0.43	0.003	0.40	0.002
C1q–IF	0.23	0.002	0.18	0.03		
Fibrinogen–IF	0.43	0.02	0.44	0.05		
Subendothelial deposits–IF	0.62	0.02	0.56	0.06		

Includes all cases with complete light microscopic, immunofluorescence (IF), and follow-up data (50 cases). Only variables significant for at least one outcome included.

Table 4. Cox proportional hazards modeling of renal relapse, CRX2, and ESRD biopsy 2

	Beta	*P*
Renal relapse		
Composite variables		
Biopsy inflammation	0.3168	0.0033
Total Ig deposits	0.0148	0.77
Chronic lesions	−0.05693	0.62
Individual variables		
Karyorrhexis/fibrinoid necrosis	0.7671	0.014
C3	0.2304	0.056
CRX2		
Composite variables		
Biopsy inflammation	0.6070	0.000009
Total Ig deposits	−0.0327	0.54
Chronic lesions	0.0906	0.36
Individual variables		
Cellular crescents	2.3457	0.00011
Macrophages in tubular lumens	2.0804	0.016
Epithelial Cells in tubular lumens	1.5379	0.0046
C3	0.6014	0.0036
ESRD		
Composite variables		
Biopsy inflammation	0.4974	0.0008
Total Ig deposits	−0.0368	0.55
Chronic lesions	0.1927	0.11
Individual variables		
Cellular crescents	3.1766	0.00074
Fibrous crescents	2.1758	0.049
Macrophages in tubular lumens	4.9381	0.0054
Epithelial Cells in tubular lumens	2.1962	0.054
C3	0.8388	0.043

Includes only cases with complete light microscopic, IF, and follow-up information (50 cases). Composite and individual variables tested separately. All Cox models are significant at $P = 0.03$ or less.

Table 5. Comparison of cases with marked hyaline deposits and minimal inflammation with other cases of diffuse proliferative lupus nephritis

	Hyaldep1 = 3 BxInfl1 < 7 (14 patients)[a]	Other diffuse proliferative (38 patients)[a]	*P*
S_{Cr}–1	139 ± 68	130 ± 78	NS
S_{Cr}–2	100 ± 29	95 ± 32	NS
S_{Cr}–3[a]	98 ± 24	167 ± 93	0.040
Proteinuria-1	4.4 ± 5.1	5.4 ± 3.8	NS
Proteinuria-2	1.2 ± 2.0	1.6 ± 1.9	NS
Proteinuria-3[a]	1.3 ± 1.2	4.5 ± 2.9	0.0060
ESRD	0.0000	0.3514	0.013
CRX2	0.0714	0.4474	0.014
Rflast	100 ± 61	261 ± 197	0.0044
Chronic Lesions Index 1	2.4 ± 2.2	3.0 ± 2.7	NS
Chronic Lesions Index 2	3.2 ± 2.4	4.2 ± 2.7	NS
Chronic Lesions Index 2[a]	3.3 ± 2.7	5.3 ± 3.3	NS
Tubular epithelial-1	3.2 ± 1.6	5.1 ± 2.5	0.014
Tubular epithelial-2	2.9 ± 1.7	4.2 ± 2.6	0.089
Tubular epithelial-3[a]	2.3 ± 1.9	4.7 ± 2.7	0.026
IFIndex-1	24.3 ± 9.2	27.9 ± 7.2	NS
IFIndex-2	17.7 ± 13.1	16.2 ± 8.2	NS
IFIndex-3[a]	16.5 ± 10.0	21.0 ± 9.0	NS
Biopsy inflammation-1	5.0 ± 1.6	7.3 ± 3.1	0.012[b]
Biopsy inflammation-2	1.3 ± 1.7	2.3 ± 1.9	0.090
Biopsy inflammation-3[a]	1.3 ± 2.1	3.6 ± 2.7	0.036

Data includes only cases with a complete follow-up.

[a] At Bx3 there were only 9 biopsies in the Hyaldep = 3 group and 18 biopsies in the other diffuse proliferative group

[b] Partly due to initial group definition

eration. However, these cases were present in sufficiently large numbers and their clinical behavior was sufficiently distinctive that sampling error could be ruled out statistically as an explanation for the overall differences.)

In humans, reversal of glomerular and interstitial fibrotic lesions has been demonstrated formally only in two other studies, both of which were focused on diabetic nephropathy [29, 30]. In one early case report the lesions in diabetic kidneys transplanted into two non-diabetic patients resolved within seven months [29]. In the other study, lesions of diabetic nephropathy reversed over a period of ten years in eight diabetic patients receiving pancreas transplantation [30]. However, ours is the first study in which diminution of fibrous lesions has been systematically demonstrated outside the transplantation setting. It must be noted, however, that two other groups have found a possible reduction of chronic lesions over successive biopsies, but both are without comment [31, 32].

Renal relapse and progression of lupus nephritis

Moroni et al found that renal relapse is associated with an extremely high rate of progression to CRX2 and ESRD [4], and this was true in our series as well. Of 56 patients who initially responded to therapy, all those who progressed to CRX2 (11 patients) suffered subsequent relapse. However, 11 of 47 patients (23.4%) who did not progress also suffered relapses. Analysis revealed that there were two interrelated differences between those who relapsed and progressed to CRX2 and those who relapsed but did not progress. First, inflammation and immune deposits in the Relapse-No CRX2 group responded as fully to therapy at Bx2 as in the No Relapse-No CRX2 group (Fig. 3 A, B), and if the limited data at Bx4 are to be believed (Fig. 4), responded once again more fully to therapy than those who progressed to CRX2. Second, chronic lesions actually declined between Bx2 and Bx3 in the Relapse-No CRX2 group whereas chronic lesions steadily progressed in the CRX2 group. Thus, the active lesions at the time of relapse were superimposed on more severe chronic lesions in the CRX2 group. One may speculate as well that the lesser reduction in inflammation at Bx2 in the CRX2 group led to ongoing damage responsible for the higher CLI at Bx3, whereas in the No CRX2 groups, inflammation was sufficiently quiescent as to permit regression of fibrous lesions.

Thus, we have partially answered one of the questions posed in the introductory comments as to how the lesions on biopsy at six months can predict events far in the future, despite the intervention of renal relapses. The initial response of inflammation and Ig deposits appears to predict how the patient will respond to possible future renal relapses. Second, the fact that chronic lesions partially revert in patients who have fully responded to therapy, whereas they continue to mount in those who do not, gives a notion of the substrate on which future relapses will be superimposed. Continuing inflammation and mounting chronic lesions also serve to partially explain why some patients simply slowly degrade their renal function without an event sufficiently dramatic to be labeled relapse.

Similarly, we found that the opposite face of relapse, failure to remit, was associated with a higher rate of CRX2 (64.8 vs. 13.0%, $P = 0.00034$). Our experience is thus comparable with that of Korbet et al, who found that failure of remission was associated with a high rate of CRX2 [6].

Role of immunoglobulin deposits and inflammatory lesions in relapse and progression

One of the striking findings in our study was that Total Ig was not significantly associated with relapse or progression, whereas BxInfl was strongly associated with progression, and C3 deposits were increasingly important with worsening disease. Other recent studies also failed to identify any prognostic significance for immune deposits [33, 34]. These observations are subject to important caveats, since neither our own nor the other studies cited examined possible differences in IgG subtypes, antibody affinity, and other variables that determine ability to elicit inflammation [17, 35].

However, even with these provisos, it has been demonstrated experimentally in two settings that the link between Ig deposits and inflammation is not obligate. First, experimentally it is possible to have substantial Ig deposits in the absence of significant inflammation and fibrosis [36, 37]. The present study presents a group of patients who are at least partially the clinical analogs of these animal models, having marked deposits but only modest inflammation, and excellent outcomes, demonstrating that it is not the absolute amount of deposits but the associated inflammation that counts in the outcome. More importantly, it is possible experimentally to produce glomerulosclerosis and interstitial nephritis in the total absence of immune deposits in lupus-prone mice genetically incapable of elaborating Ig [38], probably via B cell activation of T cells [39, 40].

Similarly, we simply have an estimation of the global quantity of inflammation in its various guises. We do not have any information about the types of infiltrating cells, as to Th1 versus Th2 lymphocytes, B cells, and macrophages, all of which have been shown to be important in determining the severity of lupus nephritis [40–43], nor do we have any way of determining what proportion of the inflammation is in direct response to immune complex deposition, and what proportion is due to other cell-mediated processes. Tentative evidence that the proportion of inflammation due to cell-mediated mechanisms was greater in the CRX2 group is the observation that at Bx1, although the levels of Ig deposits are virtually

identical in the CRX2 and No CRX2 groups (12.6 ± 5.1 vs. 13.1 ± 5.3), C3 deposits, which may be related to both humoral and cell-mediated processes, are significantly higher in the CRX2 group (6.2 ± 1.8 vs. 4.7 ± 1.7, $P = 0.0081$).

We also can eliminate one possible explanation for the simple global observation that the response of inflammation to therapy is more important than that of immune complexes. Inflammatory lesions in part represent an amplification of the effects of immunoglobulin deposits [44]. Thus, minor changes in the amount of immunoglobulins might possibly be reflected by much larger and more easily detectable changes in the inflammatory response, and hence explain the lack of significance of Ig deposits in Cox modeling. We tested this hypothesis by applying various weighting factors (2X, 10X, etc.) to Ig deposits in the Cox models and found that, although weighting Ig deposits readily changed their β-value, it did not change the probability of their association with CRX2, which never remotely approached significance.

Conclusions

Renal relapse is associated with a high rate of progression to CRX2 and ESRD, as earlier studies have shown and we have confirmed here. However, not all patients who relapse progress to CRX2. There appear to be two interrelated reasons to explain why some patients progress and others do not, despite equivalent levels of inflammatory activity on renal biopsies performed at the time of relapse. First, although data are limited, those who respond fully to therapy initially appear to respond more fully to therapy should there be a renal relapse. Second, in the group that responds fully to therapy (No CRX2), there is partial resolution of fibrotic lesions, whereas in the group with a higher level of continuing inflammation (CRX2), the chronic fibrotic lesions continue to accumulate. Hence, the substrate of chronic lesions on which the active lesions of relapse are superimposed is greater in the CRX2 group. Thus, the predictive ability of the second biopsy comes from its ability to identify a group of patients in whom the therapy has been unable to bring into check the inflammatory lesions, and who will consequently have continuing development of chronic lesions and fail to respond adequately to therapy to quell inflammatory lesions should renal relapse supervene, as unfortunately in this group it usually does.

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